intraarticularly in the knee joints or rabbits (10^7 cells/knee). Four days later, knees were lavaged and the concentration of human IRAP determined by ELISA. Values given are means $\pm$ S.D. (n=15).

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Figure 12A-C shows inhibition of IL-1 induced leukocyte infiltration in knees expressing IRAP gene. Either naive or IRAP-transduced HIG-82 cells were transplanted into rabbit knee joints, as indicated Three days later 0-100 pg/knee hIL-1β was intraarticularly injected at the indicated doses. The following day, knee joints were lavaged and the leukocytic infiltrate analyzed by counting with a hemocytometer and by cytospinning. Means $\pm$ S.E. (n=3). (A) White blood cells (WBC) per knee. (B) Stained cytospin preparation of lavages from control knee injected with IL-1. Preparation was diluted 1:10 prior to cytospinning. (C) Stained cytospin preparation of lavages from IRAP-secreting knee injected with IL-1. The preparation was not diluted.

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Figure 13 shows suppression of IL-1 induced loss of proteoglycans from articular cartilage. Either naive or IRAP-transduced HIG-82 cells were transplanted into rabbits knee joints. Three days later, 0-200 pg/knee hrIL-1 was intraarticularly injected at the indicated doses. The following day, knee joints were lavaged and the level of glycosaminoglycans (GAG) as an index of cartilage breakdown was determined.

Figure 14A-D shows suppression of IL-1 mediated synovial changes in knees expressing IRAP. Ten pg hrIL-1B was injected intraarticularly in each case. Synovia were harvested 18 hours after injection of IL-1ß, i.e. 4 days after transplantation of naive or IRAP-secreting HIG-82 cells. (A) Control synovium following injection of IL-1, magnification x 10. (B) IRAP-secreting synovium following injection of IL-1, magnification x 10. (C) Control synovium following injection of IL-1, magnification x 160. (D) IRAP-secreting synovium, magnification x 160.

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Figure 15 shows expression of human IRAP in normal and arthritic knees of rabbits. Antigen-induced arthritis was initiated by injecting 5mg ovalbumin into one knee joint (arthritic knee) of pre-sensitized rabbits on day 1. The contralateral knee (non-arthritic knee) received carrier solution only. On day 2, autologous synoviocytes (10^7/knee in 1ml saline) were transferred to selected knee joints by intraarticular injection. Certain non-arthritic knees and arthritic

knees received cells transduced with the human IRAP gene. Other non-arthritic and arthritic knees received untransduced cells or cells transduced with lac Z and neo^r genes (controls). As the results obtained with these two types of control cells were indistinguishable, they have been pooled in the figures. Detailed methods for synoviocyte culture, transduction and intraarticular implantation are disclosed throughout this specification

On day 4, knees were lavaged with 1 ml saline. On day 7, rabbits were killed and the knees again lavaged. The concentrations of human IRAP in the lavage fluids were determined by ELISA using a commercial kit (R&D Systems, Minneapolis, MN). Values given are means ± S.E. Numbers of knees are shown above each column. Asterisks denote values which differ at $p < 0.05$ (t-test).

Figure 16 shows concentrations of rabbit IL-1ß in the normal and arthritic knee joints of rabbits. Experimental conditions were identical to those described in Figure 15. However, lavage fluids were assayed for rabbit IL-1α and rabbit IL-1ß by RIA using a commercial kit (Cytokine Sciences, Boston, MA). Low levels of IL-1ß are present in non-arthritic knees as a reflection of the slight inflammatory effects provoked by intraarticular injection. No IL-1α was detectable in any of the samples. Values given are means ± S.E. Numbers of knees are shown above each column. Asterisks denote values which differ at $p < 0.05$ (t-test).

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Figure 17A-B shows the effect of IRAP gene transfer on cartilage matrix metabolism. Experimental conditions were as described for Figure 15, except that rabbits were killed both at days 4 and 7. GAG concentrations in the lavage fluids (Figure 17A) were measured spectrophotometrically by the dimethymethylene blue assay (Farndale, et al., *Biochim. Biophys. Acta.* 883: 173-177 (1986)). Fragments of articular cartilage were shaved from the femoral condyles of the knees and GAG synthesis (Figure 17B) was measured as the uptake of $^{35}SO_4^{2-}$ into macromolecular material as described (Taskiran, et al., *Biochem. Biophys. Res. Commun.* 200:142-148 (1994)). Results are shown in each case as percent of control. Values given are means ± S.E. Numbers of knees are shown above each column.

Figure 18 shows effects of IRAP gene transfer on leukocytosis. Experimental conditions were identical to those described in Figure 15. Numbers

of leukocytes in the lavage fluids were determined with a hemocytometer. Values shown are means ± S.E. Numbers of knees are shown above each column. Asterisks denote values which differ at $p < 0.05$ (t-test).

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Figure 19 A-D shows intraarticular expression of hIL-1ß and its pathogenic effects determined according to the methods of Example XVI.

Figure 20 shows levels of human (h), rabbit (r) IL-1ß and rabbit (r) TNF-α recovered in lavage fluids determined according to the methods of Example XVI. All values are expressed as the mean ± S.E.M.

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Figure 21 A-D shows detection of hIL-1β expression *in vivo* and its gross pathology determined according to the methods of Example XVI.

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Figure 22 A-F shows local and systemic effects following intraarticular transplantation of autologous hIL-1ß + synoviocytes determined according to the methods of Example XVI. 2.5 x 10^6 naive synoviocytes (Control) or hIL-1ß + synoviocytes (hIL-1) were autografted into the right and left knees, respectively, of twelve rabbits at day 0. Three rabbits were sacrificed at day 7, 4 at day 14, and 5 at day 28. For ~~a~~ A, ~~d~~ D, ~~e~~ E and ~~f~~ F each time point reflects measurements taken on remaining rabbits prior to sacrifice; ~~b~~ B, and ~~c~~ C reflect results obtained from rabbits sacrificed at that time point.

Figure 23 A-H shows joint histology following expression of hIL-1ß determined according to the methods of Example XVI. Figure 23 (~~a~~ A)-(~~f~~ F) are synovial sections stained with hematoxylin and eosin; (~~g~~ G) and (~~h~~ H) are sections of femoral condyles stained with toluidine blue.

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Figure 24~~a~~ (upper panel) shows the intraarticular expression levels of mIL-6 delivered by *ex vivo* gene transfer and Figure 24~~b~~ (lower panel) shows the effect of mIL-6 on GAG release, determined according to the methods of Example XVIII.

Figure 25~~a~~ (upper panel) shows the intraarticular elevation in leukocyte infiltration and Figure 25~~b~~ (lower panel) shows the depression of GAG synthesis rates due to over expression of mTNF-α by *ex vivo* delivery determined according to the methods of Example XVIII.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "patient" includes members of the animal kingdom including but not limited to human beings.